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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,361	03/15/2000	David Mack	A-67860-3/RMS/DAV	9370

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HOWREY SIMON ARNOLD & WHITE LLP
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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/525,361	MACK ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,52 and 55-69* is/are pending in the application.

4a) Of the above claim(s) *66-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,52 and 55-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0704*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on July 1, 2004 has been entered. Claim 48 has been added, claims 49 and 54 have been canceled, and claims 59-69 have been added. Claims 48, 52, and 55-65 are now under consideration, while claims 66-69 are withdrawn (see paragraph 3, below).

2. It is noted that the paper and computer readable forms of the Sequence Listing filed July 1, 2004 have been entered.

Election/Restriction

3. Newly submitted claims 66-69 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons. The invention of new claims 66-69 is a method of detecting polypeptides, classified in, e.g., class 435, subclass 7.1. The elected invention is a method of detecting polynucleotides, classified in, e.g., class 435, subclass 6. Thus, the invention of new claims 66-69 is classified separately from that of the invention presently under examination. Further, the invention of new claims 66-69 requires detection of polypeptides, molecules that are both structurally and

functionally distinct from the polynucleotides detected during the practice of the elected invention. Because the invention of new claims 66-69 is distinct from that of the elected invention and has acquired a separate status in the art as shown by its different classification, and because the search required for examination of new claims 66-69 is and was not required for examination of the elected invention, restriction of these inventions for examination purposes as indicated is proper.

4. Since applicant has received an action on the merits for the originally elected invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 66-69 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Specification

5. The Declaration under 37 CFR 1.132 filed July 1, 2004 is insufficient to overcome the objection to the amendment filed October 16, 2001 under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows. Applicant amended the description of Figure 10 to recite SEQ ID Nos 54, 56, 57, 59, 60, and 61, and concurrently amended the Sequence Listing to add sequences corresponding to these SEQ ID Nos. SEQ ID Nos 54, 56, 57, 59, 60, and 61 were not disclosed in the instant application as filed. It is noted that the sequences added by Applicants' amendment correspond to particular

Accession Nos. that were disclosed in Figure 10. However, the Figure does not recite the sequences. Further, the Declaration provided by Applicant does not provide actual evidence that the sequences added to the specification constitute the particular sequences that corresponded to these accession numbers at the time the invention was made. Rather, the Declaration merely contains a statement by Daniel Afar that "To the best of my knowledge" the newly added sequences correspond to the recited Accession numbers: such a statement does not constitute evidence, and Applicant has not provided, e.g., database printouts or alignments establishing the asserted correspondence. Accordingly, as Applicants' amendment introduces new matter into the specification, Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 59-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing breast cancer in a human in which increased levels of the RNA equivalent of SEQ ID NO: 23 mRNA or of another mRNA encoding the amino acid sequence of SEQ ID NO: 25, as compared to mRNA levels for these sequences in a normal human breast tissue sample, are detected in a breast tissue sample of a human patient, does not reasonably provide enablement for methods of diagnosing breast cancer using any type of sample from the patient, or for methods in which polynucleotide

levels are determined relative to any type of "normal human tissue." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses two particular BCH1 polynucleotide sequences, SEQ ID Nos 23 and 24, each of which encode the BCH1 polypeptide sequence of SEQ ID NO: 25 (see Figures 32-34 and the descriptions thereof). The specification teaches that a "high level of BCH1" is indicative of poor prognosis in individuals with breast cancer (see p. 6). The specification provides data regarding levels of BCH1 expression in breast cancer tissue samples as compared to normal control samples, and regarding a correlation between high levels of BCH1 expression and estrogen receptor localization. First, the specification provides a comparison of BCH1 expression levels in several breast cancer tissue samples as compared to a panel of controls including two samples of normal breast tissue (see Figure 36). While the data in Figure 36 indicates that BCH1 levels are higher in a few breast tumor samples than in the normal controls, the majority of the breast cancer samples appear to have exhibited levels of BCH1 expression lower than or similar to the normal breast controls. The specification does not provide further analysis of this data, or indicate, e.g., that a particular subtype of breast cancer tissues were found to exhibit consistently higher BCH1 levels than controls. Thus, the data of Figure 36 are insufficient to provide evidence that particular BCH1 levels are diagnostic for breast cancer or indicative of breast cancer prognosis. However, the

specification also provides evidence that high levels of BCH1 expression (levels of 4 or 5 on an immunohistochemical scale of 1-5) correlate with estrogen receptor (ER) localization to the cytoplasm (see p. 63). The specification discloses that "signaling through ER to activate most estrogen-responsive genes is believed to require translocation of activated ER to the nucleus," that "high expression of BCH1 is predicted to correlate with functionally-negative ER," and that "ER- correlates with poor prognosis" (see p. 63). The prior art as exemplified by Hackl et al (Anticancer Research 18(2A):839-842 [3-4/1998]) discloses that ER+ breast cancer patients "show longer disease-free intervals and a better overall survival compared to those who are" ER- (see p. 839). Further, the prior art as exemplified by Reed et al (WO 99/33869 A2 [7/1999]) discloses that an mRNA differing from that disclosed by applicant but encoding the same polypeptide is expressed at increased levels in breast cancer tissues as compared to healthy breast tissues (see Example 1 and SEQ ID NO: 56 of Reed et al; see also paragraph 20 below regarding the alignment of SEQ ID NO: 56 of Reed et al with instant SEQ ID NO: 23). Thus, the combined teachings of the specification and of the prior art provide evidence that over-expression of the BCH1 polypeptide described by applicant as SEQ ID NO: 25 is associated with breast cancer and with poor breast cancer prognosis, and indicate that increased expression of this particular BCH1 polypeptide in a breast tissue sample would be one factor that one of skill in the art would reasonably consider in diagnosis of breast cancer in a human patient. However, it is unpredictable as to whether one

of skill in the art could use applicants' invention in a manner reasonably commensurate with the instant claims.

It is noted that the evidence in the specification and in the prior art with respect to an association between increased levels of SEQ ID NO: 25/mRNAs encoding SEQ ID NO: 25 are limited to findings of altered expression in human breast tissue samples (see discussion above). Neither the specification nor the art provide evidence that one may diagnose breast cancer by detecting altered expression of these molecules in other types of biological samples (such as blood, urine, saliva, etc.). Accordingly, given the lack of guidance in the specification and in the art, it is unpredictable as to whether applicants' invention may actually be practiced successfully with biological samples other than breast tissue samples. While one of skill could conduct further experimentation to determine whether the invention could be employed successfully with other sample types, the outcome of such experimentation cannot be predicted, and it is unknown as to whether any quantity of experimentation would be sufficient to allow one of skill to use applicants' invention on other sample types. Thus, while the combined teachings of the specification and of the art would enable one of skill in the art to practice methods of diagnosing breast cancer in a human in which increased levels of the RNA equivalent of SEQ ID NO: 23 or of another mRNA encoding the amino acid sequence of SEQ ID NO: 25, as compared to mRNA levels for these sequences in a normal human breast tissue sample, are detected in a breast tissue sample of a human patient, it would require undue

experimentation for one of skill in the art to use applicants' invention in a manner reasonably commensurate with the instant claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 48, 52, and 55-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48, 52, and 55-65 are indefinite over the recitation of the limitation "an RNA equivalent" in claims 48 and 59. Neither the specification nor the art provide a clear and limiting definition for this term, and the claims are not written so as to limit them to a single, specific molecule that constitutes the RNA equivalent of SEQ ID NO: 23. It is not clear what population of molecules would be encompassed by this language, and therefore the scope of the claims is unclear.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that

the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 48, 52, 55-57, 59, and 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Khan et al (Electrophoresis 20:223-229 [2/1999]).

Reed et al disclose methods of detecting and diagnosing breast cancer in a patient in which a biological sample is obtained from the patient and in which the presence of a DNA molecule having the sequence of SEQ ID NO: 56 is detected (see entire reference, especially pages 4-5, 26-27). SEQ ID NO: 56 of Reed et al is 95.2% identical to instant SEQ ID NO: 23 (see previously provided sequence search results depicting an alignment of instant SEQ ID NO: 23 with SEQ ID NO: 56 of Reed et al). As SEQ ID NO: 56 of Reed et al encodes the same amino acid sequence as instant SEQ ID NO: 23, it is a property of SEQ ID NO: 56 of Reed et al that it encodes a "BCH1 polypeptide," as required by the claims, and further that it is an "RNA equivalent" of SEQ ID NO: 23, by virtue of encoding the same polypeptide. Reed et al disclose methods in which breast cancer is diagnosed by detecting the level of the polypeptide encoded by SEQ ID NO: 56 in a biological sample from a patient (see page 18). Reed et al teach that

SEQ ID NO: 56 was identified by performing cDNA library subtraction using a library prepared from a pool of polyA RNA from breast tumor patients and a library prepared from a pool of polyA RNA from normal human breast specimens (see Example 1, particularly pages 27-29). Reed et al further disclose that SEQ ID NO: 56 is over-expressed in breast tumor tissues and expressed at "low levels" in normal tissues (see Example 1, particularly page 30). However, Reed et al do not disclose detection of levels of SEQ ID NO: 56 in a patient or patient samples, and do not teach a method in which breast cancer is diagnosed by detecting "the level of" a polynucleotide in a patient or patient sample, as required by the claims. Khan et al disclose that human cDNA microarrays may be employed in determining the relative levels of expression of multiple genes in cancer cells simultaneously, and that such microarrays "have the particular advantage that they are readily amenable to the analysis of multiple samples" (see entire reference, particularly p. 224, left column).

In view of the teachings of Kahn et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Reed et al's method of diagnosing breast cancer by detecting the presence of SEQ ID NO: 56 in a patient sample so as to have determined the level of SEQ ID NO: 56 mRNA in a breast tissue sample from a patient using a microarray comprising a probe for specific detection of SEQ ID NO: 56 as well as probes for specific detection of other breast-cancer associated mRNAs (see p. 224-226 of Kahn et al). Reed et al disclose that SEQ ID NO: 56 may be expressed at low levels in normal tissue (see above, and p. 30 of Reed), and

thereby suggest that determination of mRNA levels (rather than mere detection of the presence of nucleic acid) may be necessary to differentiate healthy cells from cancerous cells in a sample obtained from a patient. Kahn et al disclose that their microarray method allows for simultaneous analysis of the expression of multiple genes, and facilitates the analysis of multiple samples (see entire reference, particular p. 224). Accordingly, an ordinary artisan would have been motivated to have modified the method of Reed et al so as to have determined the level of SEQ ID NO: 56 mRNA and other breast-cancer associated mRNAs in a sample in order to have differentiated between healthy cells having low level expression of SEQ ID NO: 56 and cancerous cells having increased expression of SEQ ID NO: 56, and in order to have simultaneously detected the levels of expression of other known breast-cancer associated genes, for the advantage of more accurately diagnosing the presence of breast cancer. Further, in view of the teachings of Kahn et al, an ordinary artisan would have been motivated to have made such a modification for the advantage of facilitating the analysis of multiple samples from a patient or patients, for the advantages of convenience and efficiency in analysis of samples.

Regarding claims 52, 55-56, and 61-63, it is a property of the breast tumor tissue samples of Reed et al that they comprise nucleic acids, including mRNA. Kahn et al further disclose processing of biological samples to isolate and fluorescently label RNA and it is a property of the isolated RNA that it comprises isolated mRNA (see p. 224, right column-p. 225, left column). With respect to

claims 57 and 64, Kahn et al disclose the immobilization of sample RNA on a microarray (see p. 225, left column).

13. Claims 48, 52, 59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Hackl et al (Anticancer Research 18(2A):839-842 [March-April, 1998])

Reed et al disclose methods of detecting and diagnosing breast cancer in a patient in which a biological sample is obtained from the patient and in which the presence of a DNA molecule having the sequence of SEQ ID NO: 56 is detected (see entire reference, especially pages 4-5, 26-27). SEQ ID NO: 56 of Reed et al is 95.2% identical to instant SEQ ID NO: 23 (see previously cited sequence search results depicting an alignment of instant SEQ ID NO: 23 with SEQ ID NO: 56 of Reed et al). As SEQ ID NO: 56 of Reed et al encodes the same amino acid sequence as instant SEQ ID NO: 23, it is a property of SEQ ID NO: 56 of Reed et al that it encodes a "BCH1 polypeptide," as required by the claims, and further that it is an "RNA equivalent" of SEQ ID NO: 23, by virtue of encoding the same polypeptide. Reed et al disclose methods in which breast cancer is diagnosed by detecting the level of the polypeptide encoded by SEQ ID NO: 56 in a biological sample from a patient (see page 18). Reed et al teach that SEQ ID NO: 56 was identified by performing cDNA library subtraction using a library prepared from a pool of polyA RNA from breast tumor patients and a library prepared from a pool of polyA RNA from normal human breast specimens (see Example 1, particularly pages 27-29). Reed et al further disclose that SEQ ID NO: 56 is over-expressed in breast tumor tissues and expressed at "low

levels" in normal tissues (see Example 1, particularly page 30). However, Reed et al do not disclose detection of levels of SEQ ID NO: 56 in individual patients or patient samples, and do not teach a method in which breast cancer is diagnosed by detecting "the level of" a polynucleotide in a patient or patient sample, as required by the claims. Hackl et al disclose that RT-PCR may be used to semiquantitatively determine levels of estrogen receptor (ER) and progesterone receptor (PgR) mRNA in breast tumor tissue samples obtained from patients (see entire reference, especially page 839, right column and page 840, left column). Hackl et al further teach that their mRNA detection method is more sensitive than methods of detecting protein and allows detection of ER and PgR mRNA in some instances when protein is not detected (see entire reference, especially p. 840, right column and page 841, left column).

In view of the teachings of Hackl et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Reed et al's method of diagnosing breast cancer by detecting the presence of SEQ ID NO: 56 in a patient sample so as to have determined the level of SEQ ID NO: 56 mRNA in a breast tissue sample from a patient using the semi-quantitative RT-PCR method of Hackl et al. Reed et al disclose that SEQ ID NO: 56 may be expressed at low levels in normal tissue (see above, and p. 30 of Reed), and thereby suggest that quantification of mRNA levels (rather than mere detection of the presence of nucleic acid) may be necessary to differentiate healthy cells from cancerous cells in a sample obtained from a patient. Accordingly, an ordinary artisan would have been motivated to have modified the

method of Reed et al so as to have determined the level of SEQ ID NO: 56 mRNA in a sample in order to have differentiated between a healthy cell having low level expression and a cancerous cell having increased expression, for the advantage of more accurately diagnosing the presence of breast cancer.

Additionally, in view of the teachings of Hackl et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Reed et al's method of diagnosing breast cancer by determining the level of SEQ ID NO: 56-encoded polypeptide in a patient sample so as to have determined the level of SEQ ID NO: 56 mRNA in a breast tissue sample from a patient (rather than the level of SEQ ID NO: 56-encoded polypeptide) using the semi-quantitative RT-PCR method of Hackl et al. Hackl et al disclose that RT-PCR of mRNA allows for more sensitive detection of the level of expression of a target molecule of interest that methods of detecting/quantitating protein, such as those taught by Reed et al at page 18. Accordingly, an ordinary artisan would have been motivated to have modified the method of Reed et al for the advantage of improved sensitivity in detecting the level of expression of SEQ ID NO: 56.

Regarding claims 52 and 61, it is a property of the breast tumor tissue samples of Reed et al and Hackl et al that they comprise nucleic acids, including mRNA. Hackl et al further disclose processing of biological samples to isolate RNA and amplify mRNA (see p. 839, right column and p. 840, left column), and it is a property of the isolated RNA of Hackl et al that it comprises isolated mRNA.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Primary Examiner
August 3, 2004